FIG. 1

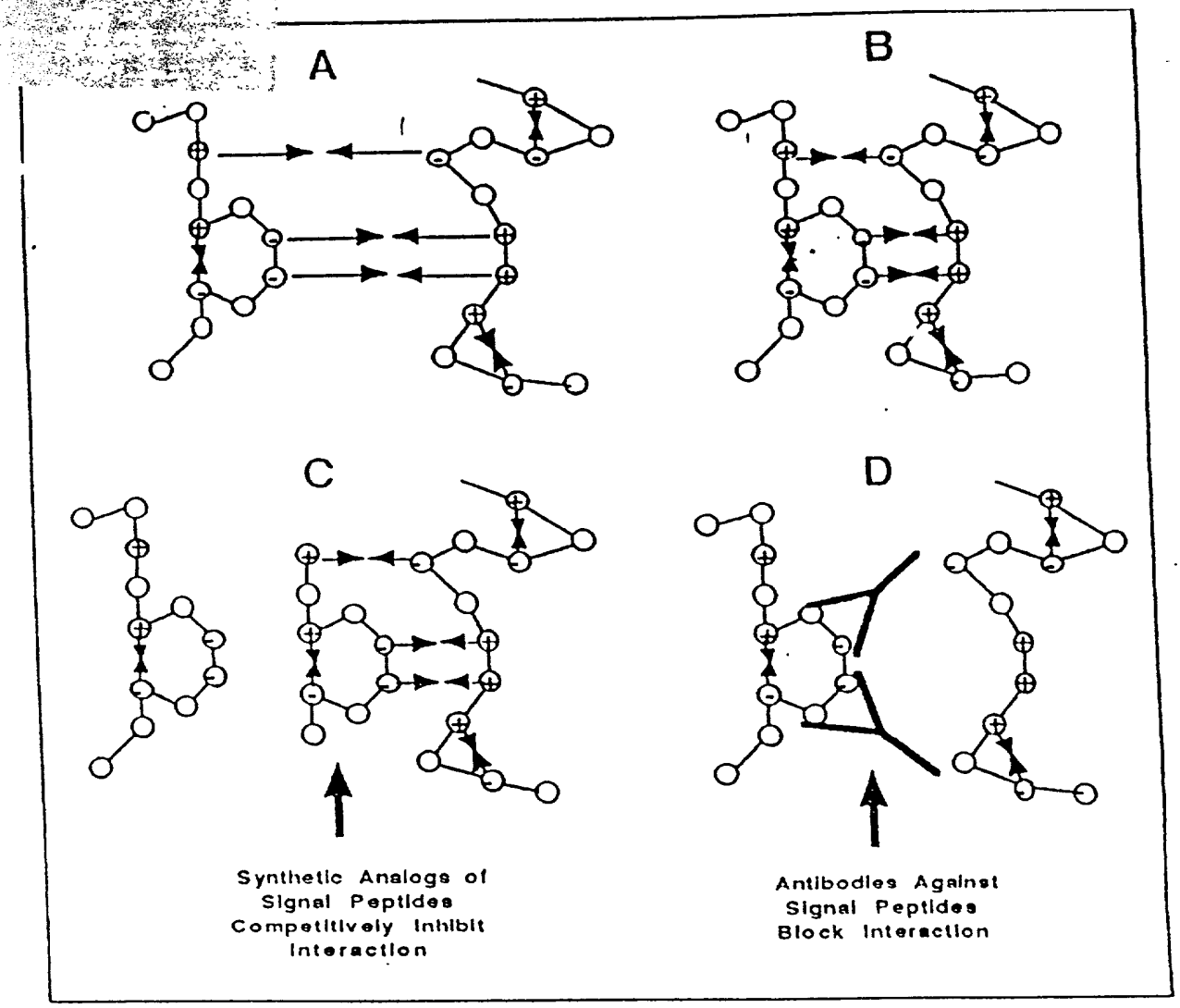
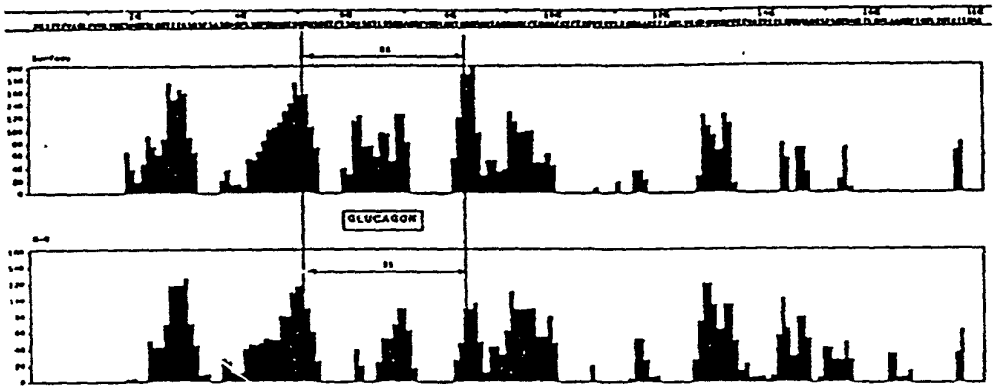

A
B
C
D
Synthetic Analogs of Signal Peptides Competitively Inhibit Interaction
Antibodies Against Signal Peptides Block Interaction

FIG. 2

Glucagon Signal Sequences And Therapeutic Use In Direct And Indirect Peptide Interception Therapy



Direct And Indirect Peptide Interception Therapy in Diabetes

- *Decrease* Effect of Glucagon
- *Increase* Relative Effect of Insulin

1. Antibodies Against Glucagon Vaccine (Synthetic Signal Oligopeptide) Decrease Action of Glucagon

2. Synthetic Analogs to Glucagon Signal Oligopeptides Competitively Inhibit Action of Glucagon

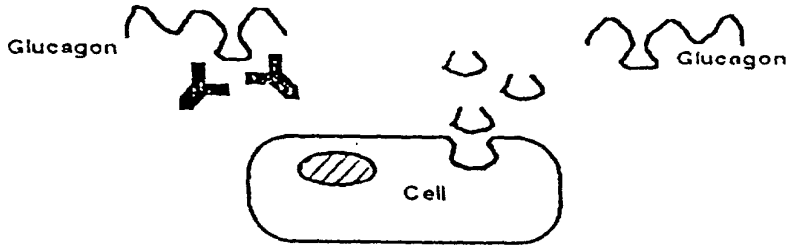


FIG. 3

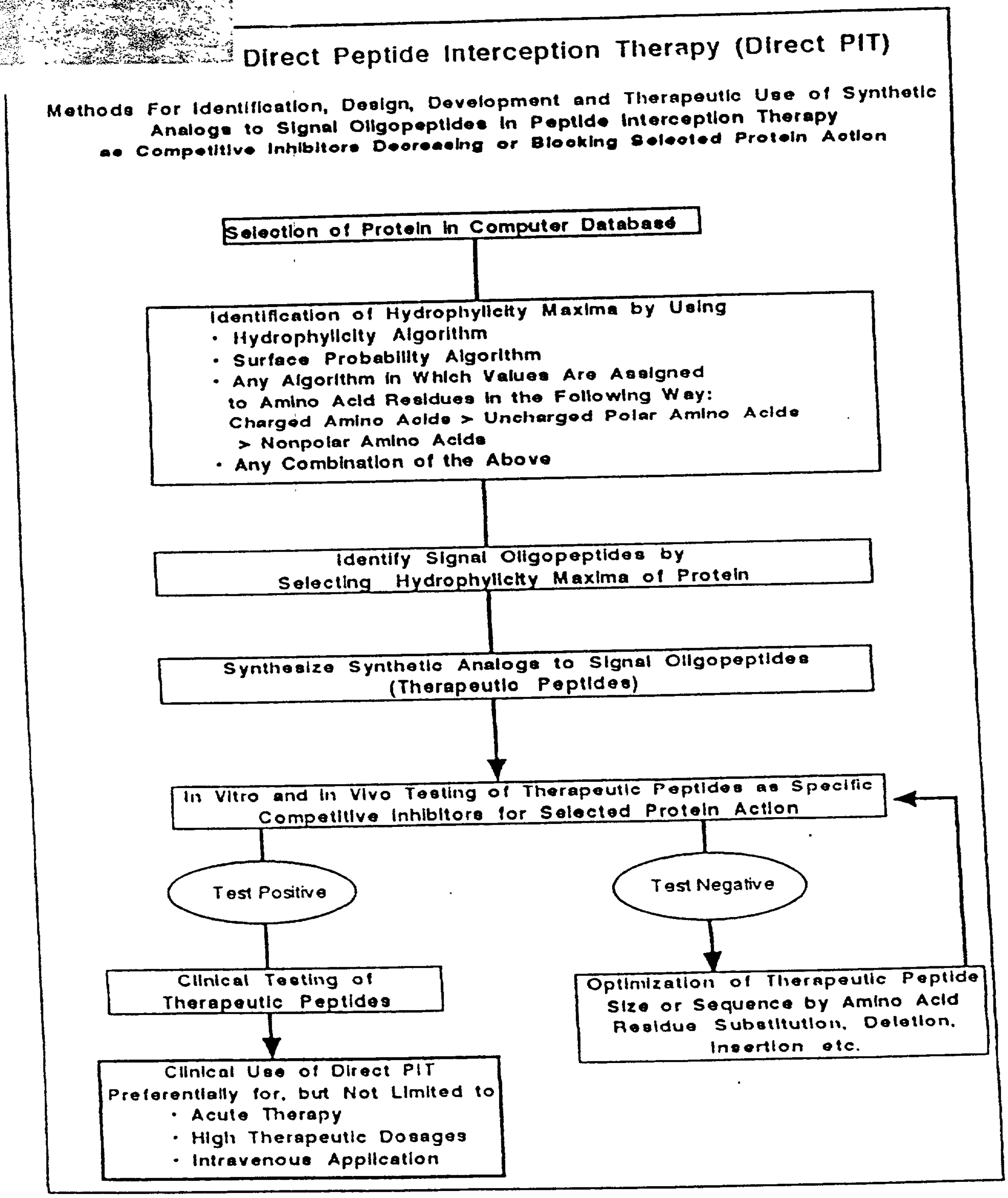

Direct Peptide Interception Therapy (Direct PIT)
Methods For Identification, Design, Development and Therapeutic Use of Synthetic Analogs to Signal Oligopeptides in Peptide Interception Therapy as Competitive Inhibitors Decreasing or Blocking Selected Protein Action
Selection of Protein in Computer Database
Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm in Which Values Are Assigned to Amino Acid Residues in the Following Way: Charged Amino Acids > Uncharged Polar Amino Acids > Nonpolar Amino Acids
• Any Combination of the Above
Identify Signal Oligopeptides by Selecting Hydrophylicity Maxima of Protein
Synthesize Synthetic Analogs to Signal Oligopeptides (Therapeutic Peptides)
In Vitro and In Vivo Testing of Therapeutic Peptides as Specific Competitive Inhibitors for Selected Protein Action
Test Positive
Test Negative
Clinical Testing of Therapeutic Peptides
Optimization of Therapeutic Peptide Size or Sequence by Amino Acid Residue Substitution, Deletion, Insertion etc.
Clinical Use of Direct PIT Preferentially for, but Not Limited to
• Acute Therapy
• High Therapeutic Dosages
• Intravenous Application

FIG. 4

Peptide Interception Therapy in the Prevention And Treatment of HIV Infections

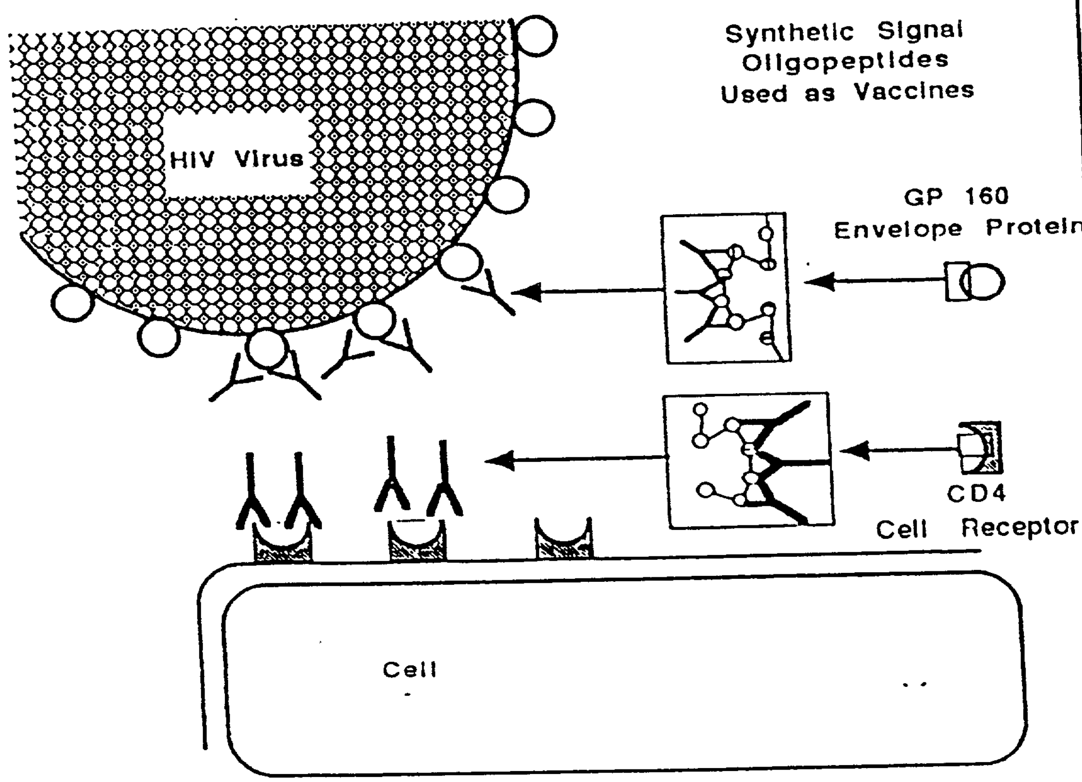


Fig 5

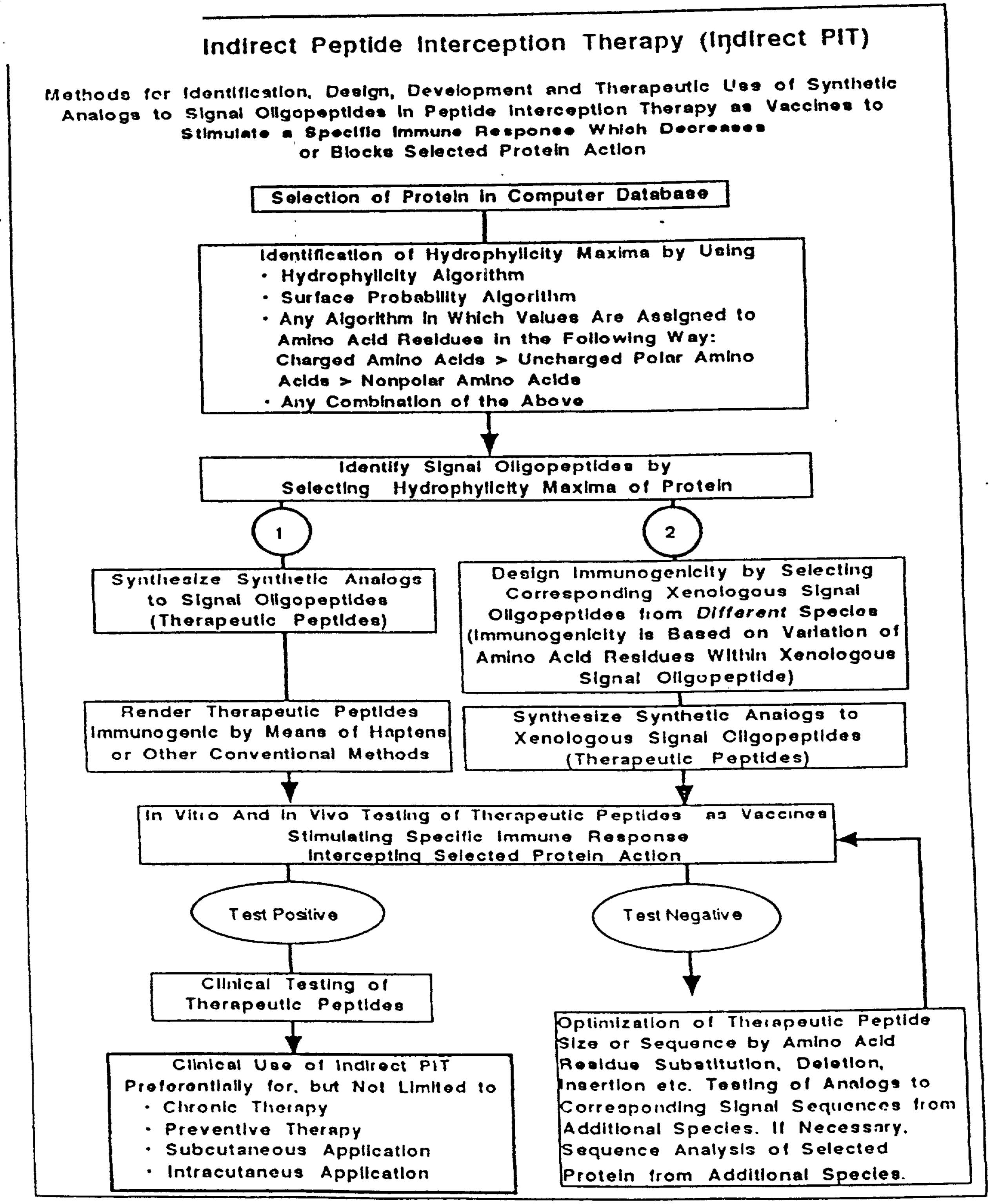

Indirect Peptide Interception Therapy (Indirect PIT)
Methods for Identification, Design, Development and Therapeutic Use of Synthetic Analogs to Signal Oligopeptides in Peptide Interception Therapy as Vaccines to Stimulate a Specific Immune Response Which Decreases or Blocks Selected Protein Action
Selection of Protein in Computer Database
Identification of Hydrophylicity Maxima by Using
• Hydrophylicity Algorithm
• Surface Probability Algorithm
• Any Algorithm In Which Values Are Assigned to Amino Acid Residues in the Following Way: Charged Amino Acids > Uncharged Polar Amino Acids > Nonpolar Amino Acids
• Any Combination of the Above
Identify Signal Oligopeptides by Selecting Hydrophylicity Maxima of Protein
1
2
Synthesize Synthetic Analogs to Signal Oligopeptides (Therapeutic Peptides)
Design Immunogenicity by Selecting Corresponding Xenologous Signal Oligopeptides from Different Species (Immunogenicity is Based on Variation of Amino Acid Residues Within Xenologous Signal Oligopeptide)
Render Therapeutic Peptides Immunogenic by Means of Haptens or Other Conventional Methods
Synthesize Synthetic Analogs to Xenologous Signal Oligopeptides (Therapeutic Peptides)
In Vitro And In Vivo Testing of Therapeutic Peptides as Vaccines Stimulating Specific Immune Response Intercepting Selected Protein Action
Test Positive
Test Negative
Clinical Testing of Therapeutic Peptides
Clinical Use of Indirect PIT Preferentially for, but Not Limited to
• Chronic Therapy
• Preventive Therapy
• Subcutaneous Application
• Intracutaneous Application
Optimization of Therapeutic Peptide Size or Sequence by Amino Acid Residue Substitution, Deletion, Insertion etc. Testing of Analogs to Corresponding Signal Sequences from Additional Species. If Necessary, Sequence Analysis of Selected Protein from Additional Species.

FIG. 6

Peptide Regulation Therapy (PRT)

Methods For Identification, Design, Development and Therapeutic Use of Synthetic Analogs to Signal Oligopeptides in Peptide Regulation Therapy as Negative Feed-Back Regulators for the Synthesis Rate of Selected Proteins

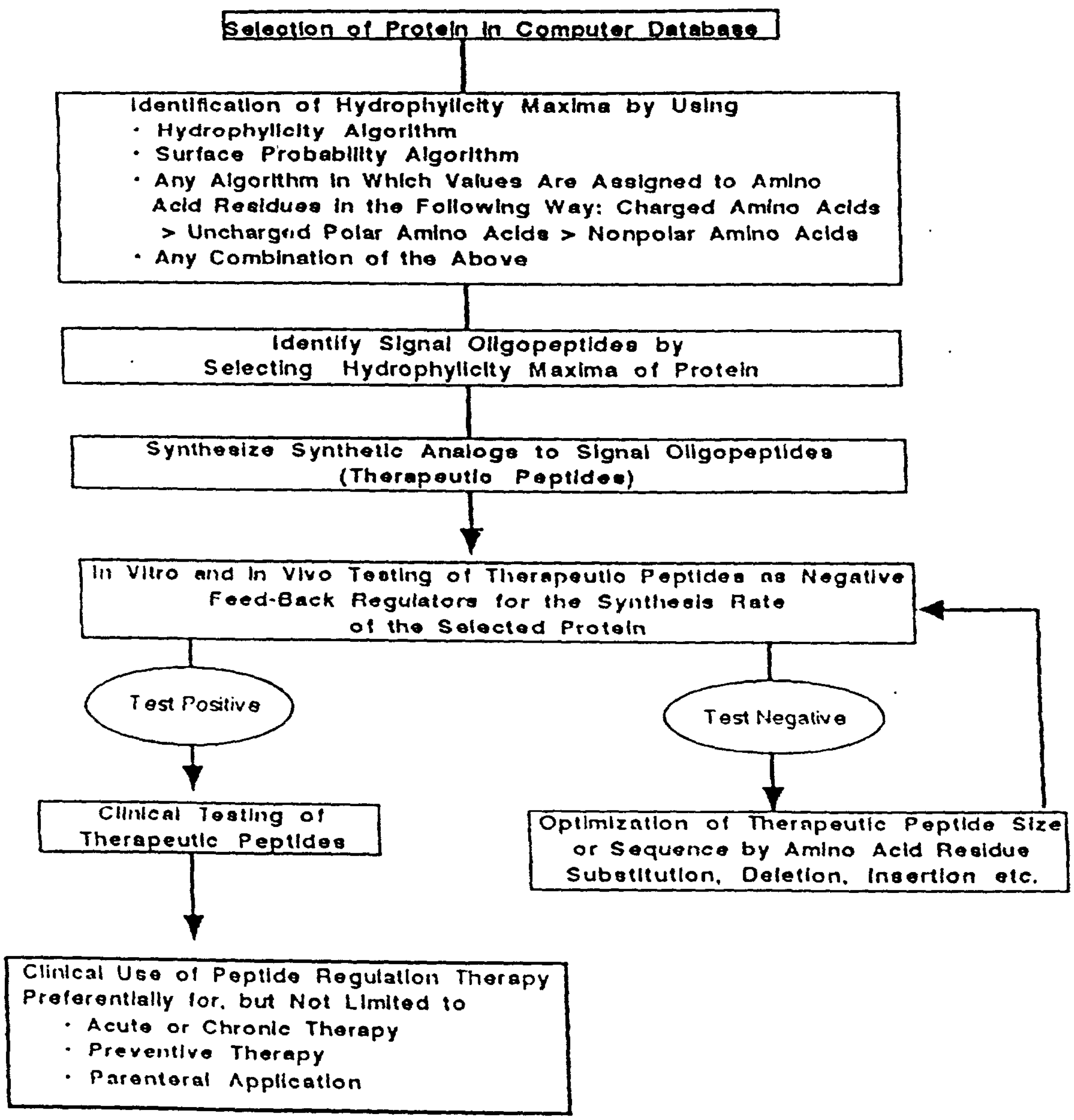


FIG. 7

Signal Oligopeptides as Antigens for the Development of Highly Specific and Precisely Characterized In Vitro Diagnostic Assays

Methods For Identification, Design, Development and Use of Synthetic Analogs to Signal Oligopeptides as Antigens for the Production of Specific Antibodies with Precise Predefined Binding Characteristics

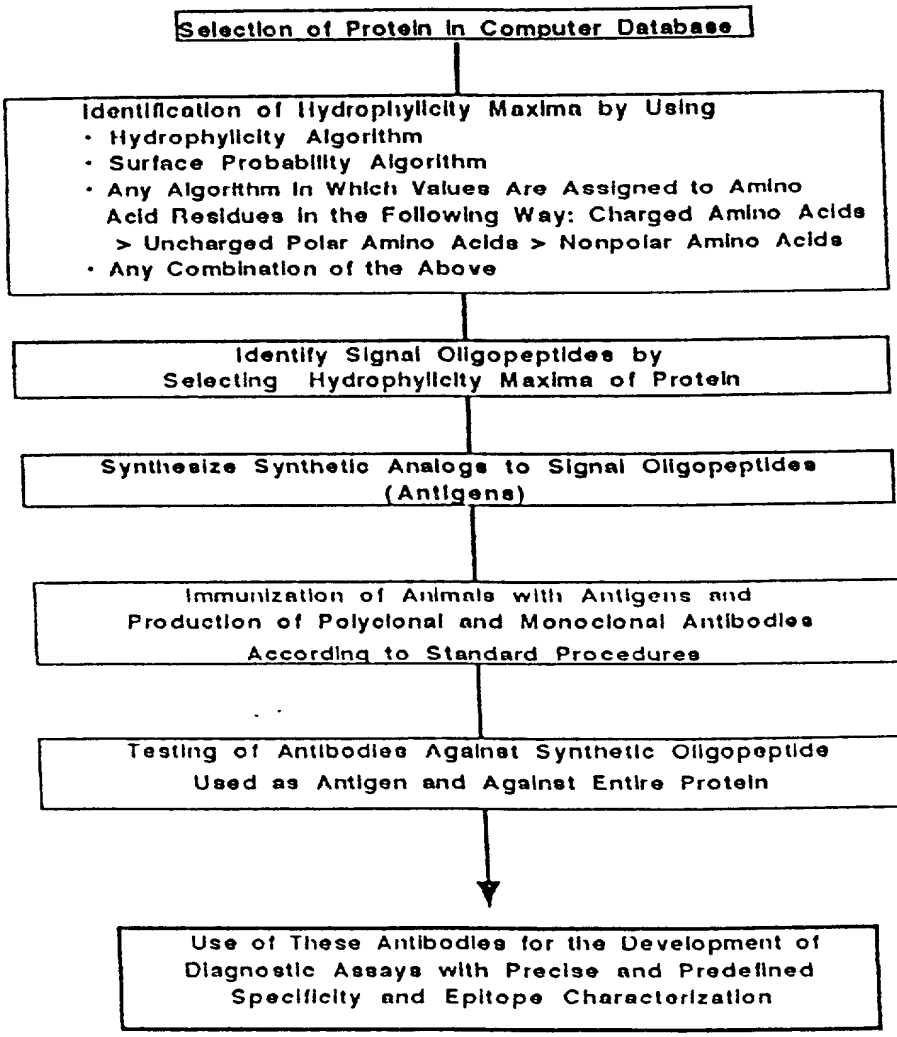
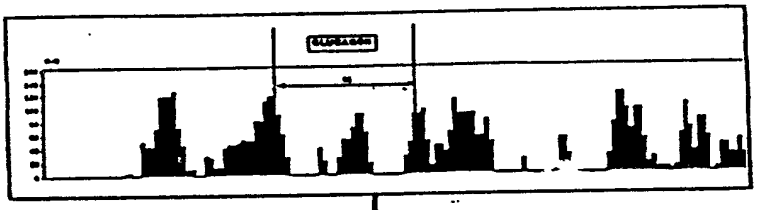


FIG. 8

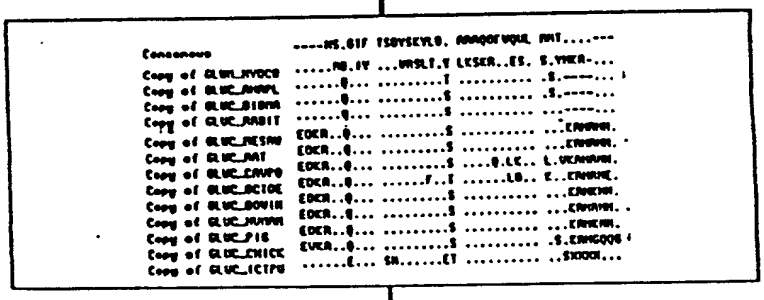
Amino Acid Sequence Selection and Therapeutic Design of Peptide Vaccines For Indirect Peptide Interception Therapy

Exemplified for the the Development of Glucagon Vaccines for Indirect Peptide Interception Therapy of Diabetes Mellitus

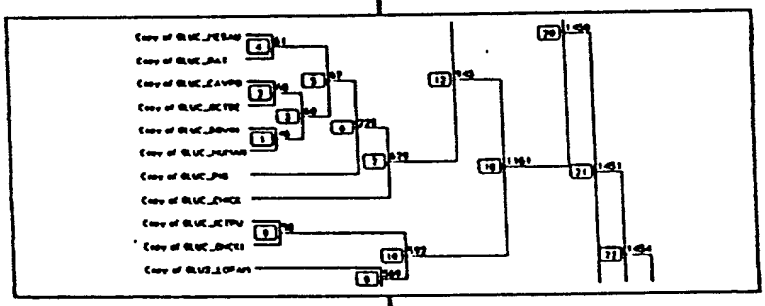
Identify Signal Oligopeptides From Hydrophylicity Maxima From Human Glucagon Precursor Sequence



Identify Corresponding Signal Oligopeptide from Glucagon *Precursor Sequences in Different Species*



Use Evolutionary Tree to Determine Relative Distance of Available Glucagon Sequences to Human Sequence. The Evolutionary Distance is Positively Correlated with Degree of Amino Acid Variation and, thus, with the Antigenicity of the Selected Protein



Select Therapeutic Peptide Sequence Among The Corresponding Signal Oligopeptide Sequences According to the Following Criteria

1. <u>Moderate Therapeutic Immune Response Desired:</u> Design of Therapeutic Peptides Analogous to Signal Sequences From Species Genetically Close to Humans (e.g. Mammals)
   - -> Amino Acid Residue Variation Within Therapeutic Peptide (Vaccine) Must Be Sufficient to Cause Immune Response
   - -> Therapeutic Use of Immune Response

2. <u>Strong Therapeutic Immune Response Desired:</u> Design of Therapeutic Peptides Analogous to Signal Sequences From Species Genetically More Distant to Humans (e.g. Fish, Yeast)
   - -> More Amino Acid Residue Variation Within Signal Sequence
   - -> Greater Antigenicity of Therap.Peptide
   - -> Higher Therapeutic Efficiency